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(54) Title: METHOD OF IMPROVED DIURESIS IN INDIVIDUALS WITH IMPAIRED RENAL FUNCTION

(57) Abstract: Disclosed is a pharmaceutical composition comprising a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic. Also disclosed are methods of inducing a diuretic effect in an animal comprising the step of administering a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a diuretic effect.

WO 2004/096228 A1

METHOD OF IMPROVED DIURESIS IN INDIVIDUALS WITH IMPAIRED RENAL FUNCTION

Field of the Invention

5 The present invention relates to the method of treatment of patients using an adenosine A₁ receptor antagonist in combination with other diuretics. The present invention also relates to pharmaceutical compositions containing the adenosine A₁ receptor antagonist in combination with other diuretics for the treatment of patients.

Summary of the Invention

10 Disclosed is a pharmaceutical composition comprising a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.

Also disclosed are methods of inducing a diuretic effect in an animal comprising the step of administering a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a
15 diuretic effect.

Detailed Description of the Preferred Embodiment

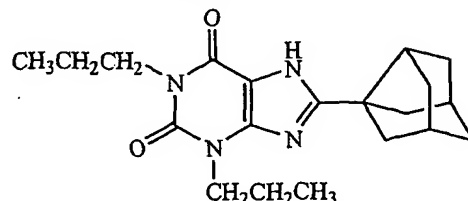
Aspects of the present invention are directed to methods of treating patients using a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic. In another aspect, the present invention is directed to
20 methods of improving diuresis while maintaining renal function in individuals with fluid overload using a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.

The term "therapeutically effective amount" as used herein refers to that amount of a composition being administered which will relieve to some extent one or more of the signs or
25 symptoms of the disorder being treated.

In certain embodiments, the individual being treated by the methods of the present invention suffers from renal impairment. In other embodiments, the individual does not suffer from renal impairment. These individuals include those who suffer from heart failure, such as congestive heart failure, or other maladies that result in fluid overload, without having yet disrupted normal
30 kidney function. In some embodiments, the individual being treated by the methods of the present invention is refractory to standard diuretic therapy. In other embodiments, the individual is not refractory to standard diuretic therapy.

Thus, in another aspect, the present invention is related to methods of preventing the deterioration of renal function in individuals comprising administering a therapeutically effective
35 amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.

KW-3902 is a xanthine-derived adenosine A₁ receptor antagonist (AA₁RA). Its chemical name is 8-(3-noradamantyl)-1,3-dipropylxanthine, also known as 3,7-dihydro-1,3-dipropyl-8-(3-tricyclo[3.3.1.0^{3,7}]nonyl)-1*H*-purine-2,6-dione, and its structure is



5

KW-3902

KW-3902 and related compounds useful in the practice of the present invention are described, for example, in U.S. Patent Nos. 5,290,782, 5,395,836, 5,446,046, 5,631,260, 5,736,528, 6,210,687, and 6,254,889.

10 A number of non-adenosine modifying diuretics are known in the art. Their examples include hydrochlorothiazides, furosemide, torsemide, bumetanide, ethacrynic acid, piretanide, norsemide, spironolactone, triamterene, metolazone and amiloridethiazides.

A significant problem encountered in treating certain conditions with individual medications is that following a course of therapy the patients become refractory to the treatment,
15 i.e., the patients begin to respond less and less to the medication until they do not respond at all. This problem is very common in patients who suffer from, for example, congestive heart failure, and are treated with diuretics.

Individual diuretics act on a specific segment of nephrons, e.g., proximal tubule, loop of Henle, or distal tubule. One mechanism by which diuretics increase urine volume is that they
20 inhibit reabsorption of sodium and accompanying water passing through the nephron. Thus, for example, a loop diuretic inhibits reabsorption in the loop of Henle. As a consequence, higher concentrations of sodium are passed downstream to the distal tubule. This initially results in a greater volume of urine, hence the diuretic effect. However, the distal portion of the tubule recognizes the increase in sodium concentration and the kidney reacts in two ways; one is to
25 increase sodium reabsorption elsewhere in the nephron; the other is to feedback via adenosine A₁ receptors to the afferent arteriole where vasoconstriction occurs. This feedback mechanism is known as tubuloglomerular feedback (TGF). This vasoconstriction results in decreased renal blood flow and decreased glomerular filtration rate (GFR). With time, these two mechanisms result in a decrease in diuretic effect and worsening of renal function. This sequence of events contributes to
30 the progression of disease.

The present inventors have discovered that the combination of KW-3902 with a standard diuretic is beneficial to patients who are refractory to standard therapy. KW-3902 also blocks the TGF mechanism mediated by adenosine (via A₁ receptors) described above. This ultimately allows

for increased GFR and improved renal function, which ultimately results in more fluid passing through the loop of Henle and the distal tubule. In addition, KW-3902 inhibits the reabsorption of sodium (and, therefore, water) in the proximal tubule, which results in diuresis. Furthermore, KW-3902 is an inhibitor of TGF, which can counteract the adverse effect of some diuretics, such as proximal diuretics, which activate or promote TGF.

The combination of the invention described herein acts synergistically to further improve renal function for continued diuresis. In addition, most CHF patients are also on additional diuretics. The combination allows for greater efficacy of other more distally acting diuretics by improving renal blood flow, renal function, and in some cases, drug delivery.

Thus, in one aspect, the present invention is related to a pharmaceutical composition comprising a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.

In some embodiments, the non-adenosine modifying diuretic is a proximal diuretic, i.e., a diuretic that principally acts on the proximal tubule. Examples of proximal diuretics include, but are not limited to, acetazolamide, methazolamide, and dichlorphenamide. Carbonic anhydrase inhibitors are known to be diuretics that act on the proximal tubule, and are therefore, proximal diuretics. Thus, in certain embodiments, the present invention relates to the combination of KW-3902 with a carbonic anhydrase inhibitor. Combinations of KW-3902 with any proximal diuretic now known or later discovered are within the scope of the present invention.

In other embodiments, the non-adenosine modifying diuretic is a loop diuretic, i.e., a diuretic that principally acts on the loop of Henle. Examples of loop diuretics include, but are not limited to, furosemide (LASIX®), bumetanide (BUMEX®), and torsemide (TOREM®). Combinations of KW-3902 with any loop diuretic now known or later discovered are within the scope of the present invention.

In yet other embodiments, the non-adenosine modifying diuretic is a distal diuretic, i.e., a diuretic that principally acts on the distal nephron. Examples of distal diuretics include, but are not limited to, metolazone, thiazides and amiloride. Combinations of KW-3902 with any distal diuretic now known or later discovered are within the scope of the present invention.

The term "pharmaceutically acceptable salt" refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reacting a compound of the invention with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Pharmaceutical salts can also be obtained by reacting a compound of the invention with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a

magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

The term "ester" refers to a chemical moiety with formula $-(R)_n-COOR'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1.

An "amide" is a chemical moiety with formula $-(R)_n-C(O)NHR'$ or $-(R)_n-NHC(O)R'$, where R and R' are independently selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), and where n is 0 or 1. An amide may be an amino acid or a peptide molecule attached to a molecule of the present invention, thereby forming a prodrug.

The term "metabolite" refers to a compound to which KW-3902 is converted within the cells of a mammal. The pharmaceutical compositions of the present invention may include a metabolite of KW-3902 instead of KW-3902. The scope of the methods of the present invention includes those instances where KW-3902 is administered to the patient, yet the metabolite is the bioactive entity.

Some of the metabolites of KW-3902 are known. These include compounds where the propyl groups on the xanthine entity are hydroxylated, or that the propyl group is an acetylmethyl ($CH_3C(O)CH_2-$) group. Other metabolites include those in which the noradamantyl group is hydroxylated (i.e., is substituted with a -OH group) or oxylated (i.e., is substituted with a =O group). Thus, examples of metabolites of KW-3902 include, but are not limited to, 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine (also referred to herein as "M1-trans"), 8-(cis-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1,3-dipropylxanthine (also referred to herein as "M1-cis"), 8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-1-(2-oxopropyl)-3-propylxanthine and 1-(2-hydroxypropyl)-8-(trans-9-hydroxy-3-tricyclo[3.3.1.0^{3,7}]nonyl)-3-propylxanthine.

Any amine, hydroxy, or carboxyl side chain on the metabolites, esters, or amides of the above compounds can be esterified or amidified. The procedures and specific groups to be used to achieve this end is known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein in its entirety.

A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further

example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety.

In another aspect, the present invention relates to a method of inducing a diuretic effect in an animal comprising identifying a patient in need thereof and administering to the patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in combination with a second pharmaceutical composition capable of inducing a diuretic effect. In some embodiments, the animal is refractory to standard diuretic therapy.

The methods of the present invention are effective in a patient. The patient may be an animal. The animal may be a mammal. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans. In some preferred embodiments, the animal is a human.

In some embodiments, the administering step comprises administering KW-3902 and the diuretic nearly simultaneously. These embodiments include those in which the two compounds are in the same administrable composition, i.e., a single tablet, pill, or capsule, or a single solution for intravenous injection, or a single drinkable solution, or a single dragee formulation or patch, contains both compounds. The embodiments also include those in which each compound is in a separate administrable composition, but the patient is directed to take the separate compositions nearly simultaneously, i.e., one pill is taken right after the other or that one injection of one compound is made right after the injection of another compound, etc. In some embodiments, a patient is infused with an intravenous formulation of one compound prior to the infusion of an intravenous formulation of the other compound. In these embodiments, the infusion may take some time, such as a few minutes, a half hour, or an hour, or longer. If the two intravenous infusions are done one right after the other, such administration is considered to be nearly simultaneously within the scope of the present disclosure, even though there was a lapse of some time between the start of one infusion and the start of the next infusion.

In other embodiments the administering step comprises administering one of KW-3902 and the diuretic first and then administering the other one of KW-3902 and the diuretic. In these embodiments, the patient may be administered a composition comprising one of the compounds and then at some time, a few minutes or a few hours, later be administered another composition comprising the other one of the compounds. Also included in these embodiments are those in which the patient is administered a composition comprising one of the compounds on a routine or continuous basis while receiving a composition comprising the other compound occasionally. In further embodiments, the patient may receive both compounds on a routine or continuous basis, such a continuous infusion of the compound through an IV line.

In some embodiments, KW-3902 is administered in a dose of 2.5 mg, 5 mg, 10 mg, 15 mg, 30 mg, 60 mg, or 100 mg, or higher. In some embodiments, the administered KW-3902 is in an injectable form, while in other embodiments, the administered KW-3902 is in a solid formulation.

5 In another aspect, the present invention relates to a method of maintaining or restoring the diuretic effect of a non-adenosine modifying diuretic in a patient comprising identifying a patient in need thereof, and administering to the patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in combination with said non-adenosine modifying diuretic.

10 In certain embodiments, the diuretic used in the methods of the present invention is furosemide. In some embodiments, furosemide is administered in a dose of 20 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg, or higher. The administration may be oral or intravenous. When furosemide is administered intravenous, it may be administered as a single injection or as a continuous infusion. When the administration is through a continuous infusion, the dosage of furosemide may be less than 1 mg per hour, 1 mg per hour, 3 mg per hour, 5 mg per hour,
15 10 mg per hour, 15 mg per hour, 20 mg per hour, 40 mg per hour, 60 mg per hour, 80 mg per hour, 100 mg per hour, 120 mg per hour, 140 mg per hour, or 160 mg per hour, or higher.

In yet another aspect, the present invention relates to a method of maintaining or restoring renal function in a patient comprising identifying a patient in need thereof, and administering a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide,
20 metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a diuretic effect.

In the context of the present disclosure, by "maintaining" renal function it is meant that the renal function, as measured by creatinine clearance rate, remains unchanged for a period of time after the start of the therapy. In other words, by "maintaining" renal function it is meant that the rate of renal impairment, i.e., the rate of decrease in the creatinine clearance rate, is slowed or
25 arrested for a period of time, however brief that period may be. By "restoring" renal function it is meant that the renal function, as measured by creatinine clearance rate, has improved, i.e., has become higher, after the start of the therapy.

30 In certain embodiments, the second pharmaceutical composition comprises a loop diuretic and a distal diuretic.

In a further aspect, the present invention relates to a method of treating a patient with a pharmaceutical composition as described herein. In some embodiments, the patient is refractory to standard diuretic therapy.

35 Certain patients who suffer from a cardiac condition, such as congestive heart failure, later develop renal impairment. The present inventors have discovered that if a patient presented with a cardiac condition, and little to no renal impairment, is treated with a pharmaceutical composition as described herein, the onset of renal impairment is delayed or arrested, compared to a patient who

receives standard treatment. Thus, aspects of the present invention relate to a method of preventing the deterioration of renal function, delaying the onset of renal impairment, or arresting the progress of renal impairment in a patient comprising identifying a patient in need thereof, and administering a therapeutically effective amount of KW-3902, or a salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.

The term "treating" or "treatment" does not necessarily mean total cure. Any alleviation of any undesired signs or symptoms of the disease to any extent or the slowing down of the progress of the disease can be considered treatment. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well being or appearance. Treatment may also include lengthening the life of the patient, even if the symptoms are not alleviated, the disease conditions are not ameliorated, or the patient's overall feeling of well being is not improved. Thus, in the context of the present invention, increasing the urine output volume, decreasing the level of serum creatinine, or increasing creatinine clearance, may be considered treatment, even if the patient is not cured or does not generally feel better.

In another aspect, the present invention relates to a method of treating a patient suffering from CHF comprising identifying a patient in need thereof, and administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a diuretic effect.

In a further aspect, the present invention relates to a method of improving overall health outcomes, decreasing morbidity rates, or decreasing mortality rates in patients comprising identifying a patient in need thereof, and administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a diuretic effect.

Overall health outcomes are determined by various means in the art. For example, improvements in morbidity and/or mortality rates, improvements in the patient's general feelings, improvements in the quality of life, improvements in the level of comfort at the end of life, and the like, are considered when overall health outcome are determined. Mortality rate is the number of patients who die while undergoing a particular treatment for a period of time compared to the overall number of patients undergoing the same or similar treatment over the same period of time. Morbidity rates are determined using various criteria, such as the frequency of hospital stays, the length of hospital stays, the frequency of visits to the doctor's office, the dosage of the medication being administered, and the like.

In some embodiments, the patient whose overall health outcome, morbidity and/or mortality rate is being improved suffers from CHF. In other embodiments, the patient suffers from renal impairment.

Other AA₁RA's are known in the art, for example, BG 9719, described in U.S. Patent Application Publication No. 2002/0115687 A1. BG 9719 is also a xanthine-derivative compound, whose structure bears some similarity to that of KW-3902. However, the present inventors have surprisingly discovered that despite the structural similarity of these compounds, they behave remarkably differently in various ways. For example, solid formulations of KW-3902 are easily obtained, and in fact disclosed in U.S. Patent No. 6,254,889. These formulations are found to be very stable at room temperature for over 3 years. Pharmacokinetic data from single administration in normal volunteers of both IV and oral dosage forms of KW-3902 show a bioavailability of ~25% for the oral dosage form and demonstrate its diuretic effect. The 20 mg oral dose group showed a 2x increase in urine volume compared to the placebo group at over the first two hours after treatment. (Unpublished clinical study data.) By contrast, literature references show that BG 9719 cannot be formulated in a solid form. For example, it has been reported that the development program for BG 9719 has "been hampered by its poor solubility and stability as well as the lack of a suitable oral formulation" (B. Ticho et al, Drug Development Research 58:486-492 (2003)).

The two compounds also show significantly different affinity for adenosine A₁ receptors and are not equally selective for adenosine A₁ receptors over adenosine A_{2a} receptors. The data for the two compounds are shown in the table below.

Compound	A ₁ K _i (nM)	A _{2a} K _i (nM)
BG 9719	0.45 ± .04	1100 ± 318
KW 3902	0.72 ± .12	108 ± 15

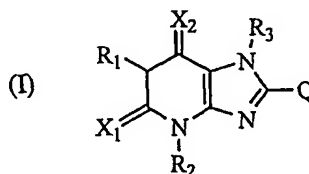
These data show BG 9719 to have a 60% great affinity for the A₁ receptor than KW-3902. Selectivity for the A₁ receptor over the A_{2a} receptor by BG 9719 is 16 times greater than selectivity by KW-3902. The data for BG 9719 were obtained from the U.S. Patent Application Publication No. 2002/0115687 A1, while the data for KW-3902 were published in Pfister, J.R., et al, *J. Med. Chem.* 1997, 40, 1773-1778.

Furthermore, at equi-potent dosages of KW-3902 and BG 9719 (unpublished clinical study data; Wolff et al, Drug Development Research 45:166-177 (1998)), when compared to placebo, KW-3902 shows significantly greater diuretic effect than BG 9719. For the purposes of the analysis below, the equi-potent dose of KW 3902 was calculated by multiplying the ratio of the A₁K_i by the dose of BG 9719 i.e. (.72/.45) x .3mg/kg = .48 mg/kg.

Compound	A ₁ K ₁ (nM)	Equi-potent Dose	% Urine volume increase over placebo, 3 hr
BG 9719	0.45 ± .04	.3 mg/kg or 20mg	33%
KW-3902	0.72 ± .12	.48mg/kg or 30mg	195%

These data collectively show that while BG 9719 and KW-3902 have some structural similarity, their pharmacokinetic activity and physiological function is quite surprisingly different, with KW-3902 providing an unexpected advantage over BG 9719.

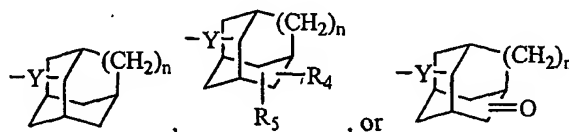
Methods of the present invention described herein may be practiced by using, instead of KW-3902, a xanthine-derivative compound of Formula I or a pharmaceutically acceptable salt thereof,



where

each of X₁ and X₂ independently represents oxygen or sulfur;

Q represents:



where Y represents a single bond or alkylene having 1 to 4 carbon atoms, n represents 0 or 1;

each of R₁ and R₂ independently represents hydrogen, lower alkyl, allyl, propargyl, or hydroxy-substituted, oxo-substituted or unsubstituted lower alkyl, and R₃ represents hydrogen or lower alkyl, or

R₄ and R₅ are the same or different and each represent hydrogen or hydroxy, and when both R₄ and R₅ are hydrogen, at least one of R₁ and R₂ is hydroxy-substituted or oxo-substituted lower alkyl,

provided that when Q is





then R₁, R₂ and R₃ are not simultaneously methyl.

In some embodiments, both of R₁ and R₂ of the compound of Formula I are lower alkyl and R₃ is hydrogen; and both of X₁ and X₂ are oxygen. In other embodiments, R₁, R₂ and R₃ independently represents hydrogen or lower alkyl. In still other embodiments, each of R₁ and R₂

independently represents allyl or propargyl and R_3 represents hydrogen or lower alkyl. In certain embodiments, X_1 and X_2 are both oxygen and n is 0.

In some embodiments, R_1 is hydroxy-substituted, oxo-substituted or unsubstituted propyl; R_2 is hydroxy-substituted or unsubstituted propyl; and Y is a single bond. In other embodiments, R_1 is propyl, 2-hydroxypropyl, 2-oxopropyl or 3-oxopropyl; R_2 is propyl, 2-hydroxypropyl or 3-hydroxypropyl.

In some embodiments Q is , while in other embodiments Q is . In other embodiments, Q is 9-hydroxy, 9-oxo or 6-hydroxy substituted 3tricyclo[3.3.1.0^{3,7}]nonyl, or 3-hydroxy-1tricyclo[3.3.1.1^{3,7}]decyl.

The term "pharmaceutical composition" refers to a mixture of a compound of the invention with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

The term "physiologically acceptable" defines a carrier or diluent that does not abrogate the biological activity and properties of the compound.

The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or suitable carriers or excipient(s). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections.

5 Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a depot or sustained release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

10 The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers
15 comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

For injection, the agents of the invention may be formulated in aqueous solutions,
20 preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable
25 the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with pharmaceutical combination of the invention, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or
30 dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt
35 thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone,

carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of
5 gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition,
10 stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention
15 are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be
20 formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may
25 take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles
30 include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

35 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

Some emulsions used in solubilizing and delivering the xanthine derivatives described above are discussed in U.S. Patent 6,210,687.

Many of the compounds used in the pharmaceutical combinations of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.* Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free acid or base forms.

Pharmaceutical compositions suitable for use in the present invention include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). Typically, the dose range of the composition administered to the patient can be from about 0.01 to 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient.

The daily dosage regimen of KW-3902 for an adult human patient may be, for example, an oral dose of between 0.1 mg and 500 mg, preferably between 1 mg and 250 mg, *e.g.* 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.01 mg and 500 mg, preferably between 0.1 mg and 200 mg, *e.g.* 1 to 100 mg of the pharmaceutical compositions of the present invention or a pharmaceutically acceptable salt thereof calculated as the free base, the composition being administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 400 mg per day. Thus, the total daily dosage by oral administration will be in the range 1 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

In certain aspects, KW-3902 is administered in conjunction with a diuretic. In these aspects, the dose of the diuretic is that which constitutes standard diuretic therapy. Those of skill in the art know what dosage of diuretics to administer to a patient in need thereof. However, because of the diuretic effect of KW-3902, the need for higher doses of the diuretic are eliminated when KW-3902 is administered to a patient in conjunction with the diuretic.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Examples

Example 1: Treatment of Individuals with Fluid Overload and Renal Impairment

A patient with fluid overload, as manifested by peripheral edema, dyspnea, and/or other signs or symptoms presents to the hospital, clinic, or doctor's office. The patient also shows some degree of renal impairment. In addition to standard of care therapy which would include IV diuretics e.g. IV furosemide, bumetanide and/or oral metolazone, the patient is also given 2.5 mg of KW-3902 in injectable form. The patient is administered 2.5 mg of KW-3902 and 40 mg of furosemide at 24 hour intervals or more frequently as needed. The patient's fluid intake and output, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, or 60 mg either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during the treatment or as the initial dose, or furosemide can be given as a continuous infusion.

Example 2: Treatment of Individuals Refractory to Standard IV Diuretic Therapy

A hospitalized patient who has been treated with maximum amounts of IV diuretic and is still symptomatic, fluid overloaded, or whose urine output is less than fluid intake is evaluated for further treatment. A 10 mg dose of KW-3902 in injectable form is infused through the IV line. The patient receives continued treatment with furosemide, and also receives 10 mg of KW-3902 at 6 hour intervals, or more or less frequently as needed. The patient's fluid intake and output, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, 60 mg, or 100 mg either during the treatment or as the initial dose, or furosemide can be given as a continuous infusion.

Example 3: Treatment of Individuals with Fluid Overload

5 A patient with fluid overload, as manifested by peripheral edema, dyspnea, and/or other signs or symptoms presents to the hospital, clinic, or doctor's office. In addition to standard of care therapy which would include IV diuretics e.g. IV furosemide, bumetanide and/or oral metolazone, the patient is also given 2.5 mg of KW-3902 in injectable form. The patient is administered 2.5 mg of KW-3902 and 40 mg of furosemide at 24 hour intervals, or furosemide can be given as a
10 continuous infusion. The patient's fluid intake and output, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, or 60 mg either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during
15 the treatment or as the initial dose. This treatment can be used for patients whether or not they suffer from renal impairment.

Example 4: Treatment of Individuals with Fluid Overload and Impaired Renal Function

A patient with fluid overload, as manifested by peripheral edema, dyspnea, and/or other signs or symptoms presents himself to the physician's office or clinic. The patient has been on a
20 therapy regimen that includes oral diuretics and, in addition, to needing a higher dose of diuretics to manage his/her fluid balance, the patient is now showing impaired renal function. The patient is prescribed 5 mg of KW-3902 to be taken orally, once daily, concurrent with other diuretic therapy. The patient's fluid intake and output, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

25 At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, 60 mg, 80 mg, or 100 mg oral either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during the treatment or as the initial dose.

Example 5: Treatment of Individuals with Fluid Overload

30 A patient with fluid overload, as manifested by peripheral edema, dyspnea, and/or other signs or symptoms presents to the physician's office or clinic. The patient has been on a therapy regimen that includes oral diuretics and needs a higher dose of diuretics to manage his/her fluid balance. To delay or prevent the onset of renal impairment and/or to delay the need to use higher dosages of standard diuretics, the patient is prescribed 5 mg of KW-3902 to be taken orally, once
35 daily, concurrent with their diuretic therapy. The patient's fluid intake and output, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, 60 mg, 80 mg, or 100 mg oral either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during the treatment or as the initial dose.

5 Example 6: Treatment of Individuals with Congestive Heart Failure

A patient with congestive heart failure presents to the physician's office or clinic. The patient is put on a therapy regimen that includes oral diuretics to manage his/her fluid balance. To delay or prevent the onset of renal impairment and/or to delay the need to use higher dosages of standard diuretics, the patient is also prescribed 5 mg of KW-3902 to be taken orally, once daily, concurrent with their diuretic therapy. The patient's fluid levels, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, 60 mg, 80 mg, or 100 mg oral either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during the treatment or as the initial dose.

15 Example 7: Improving Health Outcomes for of Individuals with Congestive Heart Failure

A patient with congestive heart failure presents to the physician's office or clinic. The patient is put on a therapy regimen that includes oral diuretics to manage his/her fluid balance. To improve overall health outcomes (i.e., morbidity or mortality rates due to CHF), the patient is also prescribed 5 mg of KW-3902 to be taken orally, once daily, concurrent with their diuretic therapy, or similar doses of KW-3902 is administered to the patient intravenously. The patient's fluid levels, urine volume, serum and urine creatinine levels, electrolytes and cardiac function are monitored.

At the discretion of the attending physician, the dosage of KW-3902 can be increased to 15 mg, 30 mg, 60 mg, 80 mg, or 100 mg either during the treatment or as the initial dose. In addition, the dosage of furosemide can be increased to 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, or 160 mg either during the treatment or as the initial dose.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, and a non-adenosine modifying diuretic.
- 5 2. The composition of claim 1, wherein the diuretic is a proximal diuretic.
3. The composition of claim 1, wherein the diuretic is a loop diuretic.
4. The composition of claim 1, wherein the diuretic is a distal diuretic.
5. The composition of claim 1 wherein the diuretic is selected from the group consisting of hydrochlorothiazides, furosemide, torsemide, bumetanide, ethacrynic acid, piretanide,
10 norsemide, spironolactone, triamterene, and amiloridethiazides.
6. A method of inducing a diuretic effect in an animal comprising
 - a) identifying a patient in need thereof, and
 - b) administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in conjunction with a
15 second pharmaceutical composition capable of inducing a diuretic effect.
7. The method of claim 6, wherein the animal is refractory to standard diuretic therapy.
8. The method of claim 6, wherein the second pharmaceutical composition is a diuretic.
- 20 9. The method of claim 8, wherein the diuretic is selected from the group consisting of hydrochlorothiazides, furosemide, torsemide, bumetanide, ethacrynic acid, piretanide, norsemide, spironolactone, triamterene, and amiloridethiazides.
10. The method of claim 8, wherein the diuretic is administered subsequent to the administration of KW-3902.
- 25 11. The method of claim 8, wherein the diuretic is administered substantially simultaneously with KW-3902.
12. The method of claim 8, wherein the diuretic is administered prior to KW-3902.
13. A method of maintaining or restoring the diuretic effect of a non-adenosine modifying diuretic in a patient comprising the administration of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in conjunction with a non-adenosine
30 modifying diuretic.
14. The method of claim 13, wherein the diuretic is furosemide.
15. The method of claim 13, wherein said patient suffers from renal impairment.
16. The method of claim 13, wherein said patient does not suffer from renal
35 impairment.
17. A method of maintaining or restoring renal function in a patient comprising
 - a) identifying a patient in need thereof, and

b) administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in combination with second pharmaceutical composition capable of inducing a diuretic effect.

5 18. The method of claim 17, wherein said second pharmaceutical composition comprises a loop diuretic and a distal diuretic.

19. A method of inducing diuresis in a patient comprising

a) identifying a patient in need thereof, and

b) administering to said patient a pharmaceutical composition of claim 1.

10 20. The method of claim 18, wherein the patient is refractory to standard diuretic therapy.

21. A method of preventing the onset of renal impairment in a patient with fluid overload or CHF, comprising

a) identifying a patient in need thereof, and

15 b) administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in conjunction with a non-adenosine modifying diuretic.

22. A method of treating a patient suffering from CHF comprising

a) identifying a patient in need thereof, and

20 b) administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in conjunction with a non-adenosine modifying diuretic.

23. A method of improving overall health outcomes, decreasing morbidity rates, or decreasing mortality rates in patients comprising

a) identifying a patient in need thereof, and

25 b) administering to said patient a therapeutically effective amount of KW-3902, or a pharmaceutically acceptable salt, ester, amide, metabolite, or prodrug thereof, in conjunction with a non-adenosine modifying diuretic.

24. The method of claim 23, wherein said patient suffers from CHF.

25. The method of claim 23, wherein said patient suffers from renal impairment.

30

INTERNATIONAL SEARCH REPORT

International Application No
.../US2004/012518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/522 A61K31/635 A61K31/63 A61P7/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 970 696 A (KYOWA HAKKO KOGYO KK) 12 January 2000 (2000-01-12) claims 1-12 tables 1,2	1-25
A	WO 99/55339 A1 (BIOGEN, INC.) 4 November 1999 (1999-11-04) claims 1-17 page 10, line 16 - line 20	1-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

26 August 2004

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/012518

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US2004/012518

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